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Role of Caudate Lobectomy in Type III_A and III_B Hilar Cholangiocarcinoma: A 15-year Experience in a Tertiary Institution

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Abstract

Background Concomitant liver resection for type III hilar cholangiocarcinoma could improve the R0 resection rate and long-term outcome. In the present study, we examine the specific role of caudate lobectomy in liver resection for type III_A and III_B hilar cholangiocarcinoma and the prognostic factors for survival in this group of patients.

Methods We reviewed all patients with type III_A and III_B hilar cholangiocarcinoma who underwent liver resection in Samsung Medical Center from January 1995 to July 2010. Patients were divided into those with and without caudate lobectomy (CL). The log rank test and Cox regression analysis were employed to investigate for prognostic factors of survival.

Results There were 127 patients in this cohort, 57 without CL (44.9%) and 70 with CL (55.1%). The demographics and symptoms of presentation were comparable. The median preoperative bilirubin level was significantly higher in the group undergoing CL ($p = 0.017$). Patients with CL had a significantly better overall survival (OS) (CL: 64.0 months vs without CL: 34.6 months) ($p = 0.010$) and disease-free survival (DFS) (CL: 40.5 months vs without CL: 27.0 months) ($p = 0.031$). Multivariate analysis showed that presence of symptoms ($p = 0.025$) and positive lymph node (LN) metastasis ($p < 0.001$) were negative prognostic factors for OS. Furthermore, multivariate analysis for DFS found that caudate lobectomy ($p = 0.016$) and positive LN metastasis ($p = 0.001$) were positive and negative prognostic factors, respectively.

Conclusions Caudate lobectomy contributed to improvement of DFS and OS in type III hilar cholangiocarcinoma. Other prognostic factors include positive LN metastasis and presence of symptoms.

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Introduction

Hilar cholangiocarcinoma is the most common malignancy arising from the biliary system. This tumor is located in the vicinity of bile duct bifurcation in the hepatic hilum. The close proximity of the tumor to the portal vein, hepatic arteries, and liver parenchyma poses a great challenge in achieving oncological clearance without radical resection [1]. Prior to the 1990s, hepatic resection was not recommended for treatment of hilar cholangiocarcinoma because of the associated high morbidity and mortality rate [2, 3]. With the improvement of preoperative care, surgical techniques, and postoperative management, aggressive approaches, including extended liver resection, have gained much popularity. The Japanese surgeons were the first to popularize this treatment, showing the clear improvement in resectability and long-term survival with the use of major hepatectomy in surgical treatment of hilar cholangiocarcinoma [4–9].

Vertical extension of tumor into the caudate duct is commonly seen in hilar cholangiocarcinoma, particularly in type III and IV hilar cholangiocarcinoma (based on the Bismuth-Corlette classification) [10, 11]. This is due to the lack of a strong muscular layer to restrict the tumor extension. In addition, caudate biliary ducts usually enter the main bile duct at the confluence posteriorly. Therefore, concomitant resection of the liver parenchyma, including the caudate lobe, could improve the negative resection margin rate. However, extended resection of liver leading to postoperative hepatic insufficiency remains a real concern as it increases the risk of morbidity and mortality. To increase the likelihood of successful extended liver resection, portal vein embolization could be employed.

Many studies have reported the feasibility of performing extended liver resection, including caudate lobectomy (CL), with good long-term results. However, there are few reports on the specific role of CL in extended liver resection, specifically in type III_A and III_B hilar cholangiocarcinoma. Therefore, the primary aim of the present study was to evaluate the long-term outcome of concomitant caudate lobectomy as part of liver resection in type III_A and III_B hilar cholangiocarcinoma. We also studied the prognostic factors of survival in type III_A and III_B hilar cholangiocarcinoma.

Patients and methods

A retrospective data collection of all patients who underwent liver resection for hilar cholangiocarcinoma in Samsung Medical Center, South Korea, from January 1995 to July 2010 was performed. During this period, there were 236 patients with hilar cholangiocarcinoma who underwent surgical resection. As resectable type IV hilar cholangiocarcinoma required extended hepatectomy with concomitant caudate lobectomy, they were not selected for analysis in this study. Thus, there were 131 patients in this cohort whose disease was classified as type III_A and III_B based on the Bismuth-Corlette classification. After excluding four patients who underwent segmental resection of the extrahepatic bile duct only, there were 127 patients with liver resection performed for type III_A and III_B hilar cholangiocarcinoma who were suitable for analysis. We examined the role of concomitant CL in the liver resection in this group of patients.

All tumors were discussed at a multidisciplinary meeting with the radiologists, to identify location of tumor, staging, and resectability. The emphasis was to rule out distant metastasis or major vascular encasements on imaging studies. Computed tomography volumetry was performed to study the adequacy of the remnant liver after resection. Ideally, the remnant liver should be at least 20% of the total liver volume. In patients with borderline resectability due to limited remnant liver (volume of remnant liver less than 20%), we performed portal vein embolization (PVE) to induce hypertrophy of the remnant liver.

Patients with hilar cholangiocarcinoma were usually deeply jaundiced, indicating a high level of bilirubin, which could intoxicate hepatocytes and impair liver regeneration. Therefore, when the serum bilirubin level was more than 3.0 mg/dl, we performed preoperative biliary drainage (PBD) to relieve the biliary obstruction on the liver remnant side. Percutaneous transhepatic biliary drainage (PTBD) was the usual route for decompression. The half of liver intended for resection was decompressed if the patient remained severely jaundiced or developed cholangitis. Portal vein embolization was performed when the serum bilirubin level dropped to below 7.0 mg/dl after PTBD. Endoscopic retrograde cholangiopancreatography (ERCP) was useful in both its diagnostic and therapeutic roles in terms of delineating the anatomy of biliary tree and achieving cytology when malignancy was doubtful. Endoscopic retrograde biliary drainage (ERBD) and endoscopic nasal biliary drainage (ENBD) were performed to facilitate preoperative biliary drainage. However, they were unsuccessful in many cases of the type III and IV hilar cholangiocarcinoma because of the location of the tumor high within the liver hilum, and because of the severity of obstruction.

Criteria for resectability of hilar cholangiocarcinoma was follows: the absence of (1) peritoneal or liver metastases; (2) massive ingrowth into contralateral branch of portal vein or into the main stem, (3) infiltration of the main hepatic artery or its branch(es) to the contralateral liver segments, (4) atrophy of the contralateral liver lobe, and (5) lymph node involvement outside the hepatic hilar region. Operative technique for hilar cholangiocarcinoma was previously described [12]. Ligamentous attachment of the liver was taken down and thorough intraoperative ultrasonography was performed to rule out metastasis. The liver, including the caudate lobe if necessary, was mobilized. The liver hilum was dissected to identify the necessary vascular structures to preserve while ligating and dividing those on the side to be removed. Routine lymph node dissection (LND) was performed to removal lymphatic tissue around the hepatoduodenal ligament up to the level of coeliac axis. Parenchyma transection was performed with the Cavitron Ultrasonic Aspirator (CUSA) device. Intraoperative frozen biopsy for proximal and distal bile ducts was performed to determine the resection margin status and radicality of operation. Caudate lobectomy was performed as an extension of the liver resection if the surgeon felt that it was required to obtain greater oncological clearance. Following resection, Roux-en-Y bilioenteric anastomosis was routinely performed to restore the biliary flow pathway. The AJCC (American Joint Committee on Cancer) staging system, 7th edition, was applied to this cohort of hilar cholangiocarcinoma patients [13]. Tumor sizes, stages, and radicality were documented. This was useful for determining the necessity for adjuvant therapy.

After surgical treatment, patients were followed closely at 4-monthly intervals in the outpatient clinic. Follow-up included routine physical examination and radiologic and laboratory investigations. Studies that were performed included computed tomography (CT) scan of abdomen and pelvis to evaluate local and systemic recurrence. Tumor markers such as carcinoembryonic antigen (CEA) and CA 19-9 were assayed. In suspected recurrence, further investigations such as positron emission tomography (PET) scan were employed to assess extra-abdominal systemic recurrence.

In this study, overall survival (OS) was analyzed as the time from the date of hepatectomy until the date of death (i.e., death from all causes, including dead-of-disease [DOD] and dead-of-other-causes [DOC]), whichever occurred first. Patients lost to follow-up or in whom the event of interest had not yet been observed were censored at the date last known to be alive.

A total of 127 cases with liver resection for type III_A and III_B hilar cholangiocarcinoma were accrued during the study period. Patients were divided into two groups, those without CL and those with CL concomitantly with the liver resection. The data were analyzed with SPSS (version 17.0). Statistical significance was set at $p < 0.05$. The chi square test was used

Table 1 Demographic features of patients with type III_A and III_B hilar cholangiocarcinoma in this cohort ($n = 127$)

Factors	All ($n = 127$)	Without CL ($n = 57$)	With CL ($n = 70$)	p value
Age, years, median (range)	62.0 (41.0–79.0)	62.0 (42.0–75.0)	63 (41.0–79.0)	0.215
Age ≤ 60 years	55 (43.3%)	25 (43.9%)	30 (42.9%)	0.910
Age > 60 years	72 (56.7%)	32 (56.1%)	40 (57.1%)	
Gender				
Male	77 (60.6%)	36 (63.2%)	41 (58.6%)	0.599
Female	50 (39.4%)	21 (36.8%)	29 (41.4%)	
Bismuth-Corlette classification				
Type III_A hilar cholangiocarcinoma	94 (74.0%)	39 (68.4%)	55 (78.6%)	0.195
Type III_B hilar cholangiocarcinoma	33 (26.0%)	18 (31.6%)	15 (21.4%)	
Symptomatic vs asymptomatic				
Asymptomatic	24 (18.9%)	11 (19.3%)	13 (18.6%)	0.917
Symptomatic	103 (81.1%)	46 (80.7%)	57 (81.4%)	
Abdominal pain	32 (25.2%)	15 (26.3%)	17 (24.3%)	0.429
Jaundice	54 (42.5%)	20 (35.1%)	34 (48.6%)	
Indigestion	8 (6.3%)	6 (10.5%)	2 (2.9%)	
Fever/chills	4 (3.1%)	2 (3.5%)	2 (2.9%)	
General weakness	4 (3.1%)	2 (3.5%)	2 (3.5%)	
Weight loss	1 (0.8%)	1 (1.8%)	0 (0.0%)	
Risk factors of cholangiocarcinoma				
History of biliary stone	13 (10.3%)	6 (10.5%)	7 (10.1%)	0.944
Chronic hepatitis B status	5 (3.9%)	3 (5.3%)	2 (2.9%)	0.488
Background of cirrhosis	4 (3.1%)	1 (1.8%)	3 (4.3%)	0.417
History of clonorchis saneness	4 (3.1%)	3 (5.3%)	1 (1.4%)	0.218
Period when operation performed				
Before 2005	46 (36.2)	37 (64.9)	9 (12.9)	<0.001
After 2005	81 (63.8)	20 (35.1)	61 (87.1)	
Types of liver resection				
Extended right hepatectomy	35 (27.5)	0 (0.0)	35 (50.0)	
Right hepatectomy	48 37.8)	32 (56.1)	16 (22.9)	
Extended left hepatectomy	10 (7.9)	0 (0.0)	10 (14.3)	
Left hepatectomy	24 (21.3)	19 (33.3)	5 (7.1)	
Hepatopancreaticoduodenectomy	10 (7.9)	6 (10.5)	4 (5.7)	

* $p < 0.05$ as statistically significant

CL caudate lobectomy

in cross tabulation of nominal data. Student's *t*-test was performed for parametric continuous variables, and the Mann–Whitney test was used for nonparametric continuous variables. Kaplan–Meier analysis was used to depict the overall survival and difference in survival between study groups. Factors found to be significant on univariate analysis for both OS and DFS were subjected to multivariate analysis using Cox proportional hazard model to determine the significant prognostic value of the factors.

Results

Of the 127 patients accrued, 57 patients (44.9%) did not have CL and 70 patients (55.1%) did have CL performed as part of the liver resection.

Demography and characteristics of patients with and without CL

The age and gender distribution of patients in the two groups were comparable ($p = 0.215$ and $p = 0.599$, respectively). Three quarters of the cases were type III_A hilar cholangiocarcinoma ($n = 94$; 74.0%) and 33 patients (26.0%) had type III_B hilar cholangiocarcinoma. Distribution of tumor within each group was similar ($p = 0.195$) (Table 1). In less than one fifth of the patients (18.9%) tumor was detected incidentally without any symptoms. There was no difference between the two groups in terms of risk factors of cholangiocarcinoma (Table 1). The type of liver resection performed is shown in Table 1. There were significantly more patients with caudate lobectomy in the period after 2005 ($n = 61$; 87.1%) compared to those

Table 2 Preoperative parameters and postoperative adjuvant and recurrence rate in the study cohort ($n = 127$)

Factors	All patients ($n = 127$)	Without CL ($n = 57$)	With CL ($n = 70$)	p value
Preoperative biliary drainage	76 (59.8%)	34 (59.6%)	42 (60.0%)	0.968
Types of PBD				
PTBD	42 (33.1%)	21 (36.8%)	21 (30.0%)	0.442
ERBD	9 (7.1%)	3 (5.3%)	6 (8.6%)	
ENBD	19 (15.0%)	6 (10.5%)	13 (18.6%)	
Stent	2 (1.6%)	2 (3.5%)	0 (0.0%)	
Combination of methods	4 (3.1%)	2 (3.5%)	2 (2.9%)	
Preoperative PVE	14 (11.0%)	4 (7.0%)	10 (14.3%)	0.193
Preoperative blood parameters				
Bilirubin level, median (range)	3.0 (0.3–36.8)	2.1 (0.4–21.9)	4.2 (0.3–6.8)	*0.017
Bilirubin ≤3.0	65 (51.2%)	33 (57.9%)	32 (45.7%)	0.172
Bilirubin >3.0	62 (48.8%)	24 (42.1%)	38 (54.3%)	
CA 19-9 level, median (range)	82.3 (0.1–76,150.0)	133.0 (1.0–48,095.0)	70.7 (0.1–76150.0)	0.248
CA 19-9 ≤ 37 U/ml	36 (32.4%)	14 (29.8%)	22 (34.4%)	0.610
CA 19-9 > 37 U/ml	75 (67.6%)	33 (70.2%)	42 (65.6%)	
CEA level, median (range)	1.8 (0.2–18.9)	2.0 (0.5–18.9)	1.7 (0.2–16.1)	0.217
CEA ≤ 5.0 U/ml	88 (93.6%)	37 (92.5%)	51 (94.4%)	0.703
CEA > 5.0 U/ml	6 (6.4%)	3 (7.5%)	3 (5.6%)	
Duration of operation, min	390 (200–725)	420 (200–725)	373 (238–580)	0.146
Postoperative length of stay, days	16 (7–102)	20 (7–93)	13 (7–102)	0.128
90-day/in-hospital mortality	3 (2.4%)	2 (3.5%)	1 (1.4%)	0.443
Morbidity	8 (6.3)	5 (8.8)	3 (4.3)	0.301
Pneumonia	1 (12.5)	1 (20.0)	0 (0.0)	
Bile leak and recurrent cholangitis	2 (25.0)	0 (0.0)	2 (67.7)	
Postoperative hemorrhage	5 (62.5)	4 (80.0)	1 (33.3)	
Postoperative adjuvant treatment	43 (33.9%)	21 (36.8%)	22 (31.4%)	0.521
Recurrence rate	50 (39.4%)	24 (42.1%)	26 (37.1%)	0.569
Duration of follow-up, (days), median (range)	24.7 (9.1–148.2)	26.0 (9.1–148.2)	22.8 (6.7–89.7)	0.346

* $p < 0.05$ as statistically significant

PVE portal vein embolization; *PBD* preoperative biliary drainage; *PTBD* percutaneous transhepatic biliary drainage; *ERBD* endoscopic retrograde biliary drainage; *ENBD* endoscopic nasal biliary drainage; *CEA* carcinoembryonic antigen without caudate lobectomy prior to 2005 ($n = 37$; 64.9%) ($p < 0.001$).

Preoperative and postoperative parameters

Close to 60% of patients (59.8%) required PBD in this cohort. The most common mode of PBD was PTBD in both groups (without CL: 36.8% and with CL: 30.0%). Although the proportion of PVE in those with CL (14.3%) was double that without CL (7.0%), this was not found to be statistically significant ($p = 0.193$). The median preoperative bilirubin level was significantly higher for patients with CL (median: 4.2, 0.3–36.8 mg/dl) as compared to those without CL (median: 2.1, 0.4–21.9 mg/dl) ($p = 0.017$). The median tumor marker levels such as CA 19-9 and CEA were comparable between the two groups ($p = 0.248$ and $p = 0.217$, respectively) (Table 2).

About one third of all patients received adjuvant chemotherapy (gemcitabine-based regimen) following surgery in both groups (without CL: 36.8% and with CL: 31.4%; $p = 0.521$). Two fifths of the patients (42.1%) in the group without CL experienced recurrence during the study period, as compared to 37.1% in the group with CL ($p = 0.569$) (Table 2).

The 90-day in-hospital mortality rate was comparable between the two groups (without CL: 3.5% vs with CL: 1.4%; $p = 0.443$). The morbidity rate was also comparable between the two groups (Table 2).

Pathological factors

The median tumor size was comparable between the two groups ($p = 0.600$). Close to three quarters of patients in both groups had T1 and T2 stage of disease (without CL: 71.9% and with CL: 72.9%; $p = 0.907$). The proportion of

Table 3 Pathological features of patients in the study cohort ($n = 127$)

Factors	All patients ($n = 127$)	Without CL ($n = 57$)	With CL ($n = 70$)	p value
Tumor size, cm, median (range)	2.5 (1.0–11.0)	2.9 (1.0–11.0)	2.5 (1.4–6.0)	0.600
Tumor ≤5.0 cm	111 (91.0%)	51 (89.5%)	60 (92.3%)	0.586
Tumor >5.0 cm	11 (9.0%)	6 (10.5%)	5 (7.7%)	
T-stage of tumor				
T1	17 (13.4%)	8 (14.0%)	9 (12.9%)	0.994
T2	75 (59.1%)	33 (57.9%)	42 (60.0%)	
T3	33 (26.0%)	15 (26.3%)	18 (25.7%)	
T4	2 (1.6%)	1 (1.8%)	1 (1.4%)	
Stratified T-stage				
T1 and T2	92 (72.4%)	41 (71.9%)	51 (72.9%)	0.907
T3 and T4	35 (27.6%)	16 (28.1%)	19 (27.1%)	
Nodal status				
N0	77 (66.4%)	33 (68.8%)	44 (64.7%)	0.650
N1	39 (33.6%)	15 (31.3%)	24 (35.3%)	
Number of LN harvested, median (range)	11 (0–42)	9 (1–27)	13 (0–42)	*0.030
Number of LN involved, median (range)	0 (0–13)	0 (0–6)	0 (0–13)	0.382
AJCC 7th edition staging				
Stage I	18 (15.7%)	9 (18.8%)	9 (13.4%)	0.925
Stage II	40 (34.8%)	16 (33.3%)	24 (35.8%)	
Stage IIIA	18 (15.7%)	8 (16.7%)	10 (14.9%)	
Stage IIIB	37 (32.2%)	14 (29.2%)	23 (34.3%)	
Stage IVA	2 (1.7%)	1 (2.1%)	1 (1.5%)	
Grade of differentiation				
Well differentiated	15 (14.2%)	8 (16.0%)	7 (12.5%)	0.461
Moderately differentiated	64 (60.4%)	32 (64.0%)	32 (57.1%)	
Poorly differentiated	27 (25.5%)	10 (20.0%)	17 (30.4%)	
Lymphovascular invasion	21 (60.0%)	9 (64.3%)	12 (57.1%)	0.673
Perineural invasion	75 (91.5%)	33 (91.7%)	42 (91.3%)	0.954
Positive resection margin (R1)	15 (11.8%)	9 (15.8%)	6 (8.6%)	0.210

* $p < 0.05$ as statistically significant

AJCC American Joint Committee on Cancer, *LN* lymph nodes patients with N1 nodal metastasis in the CL group was 35.3% ($n = 24$), comparable to those without CL ($n = 15$, 31.3%) ($p = 0.650$). However, the median number of lymph nodes harvested was significantly higher in the group with CL (without CL, median: 9, 1–27 and with CL, median: 13, 0–42) ($p = 0.030$).

Although the rate of positive resection margin in patients without CL was double (15.8%) that of patients with CL (8.6%), this difference was not found to be statistically significant ($p = 0.210$). There was also no difference in the distribution of disease stages based on 7th edition of AJCC classification of hilar cholangiocarcinoma in this cohort (Table 3).

Prognostic factors of overall survival (OS) (Table 4)

The overall median duration of follow-up in this cohort was 24.7 months (range: 9.1–148.2 months). The median follow-up period comparing with CL and without CL was similar ($p = 0.346$) (Table 2).

Patients with CL were found to have significantly longer OS in this study. The median OS in patients with CL was 64.0 months as compared to 34.6 months in those without CL ($p = 0.011$). The 1-, 3-, 5- and 7-year OS rates were 76.0, 70.0, 66.0, and 66.0%, respectively, in patients with CL, in contrast with 61.0, 46.0, 30.0and 30.0%, respectively, in patients without CL (Fig. 1a).

On univariate analysis for OS using the log-rank test, caudate lobectomy (Hazard Ratio [HR]: 0.470, $p = 0.010$), operation period after 2005 (HR: 0.254, $p = 0.009$), symptomatic patients (HR: 5.026, $p = 0.007$), preoperative CA 19-9 > 37.0 U/ml (HR: 2.187, $p = 0.036$), preoperative CEA > 5.0 U/ml (HR: 3.060, $p = 0.003$), tumor size > 5 cm (HR: 2.738, $p = 0.015$), stratified T-stage (T3 and T4) (HR: 1.796, $p = 0.036$), positive LN metastasis (HR: 2.825, $p = 0.001$), positive resection margin (HR: 2.099, $p = 0.029$), and presence of lymphovascular invasion (HR: 3.850, $p = 0.042$) were found to have significant impact on overall survival.

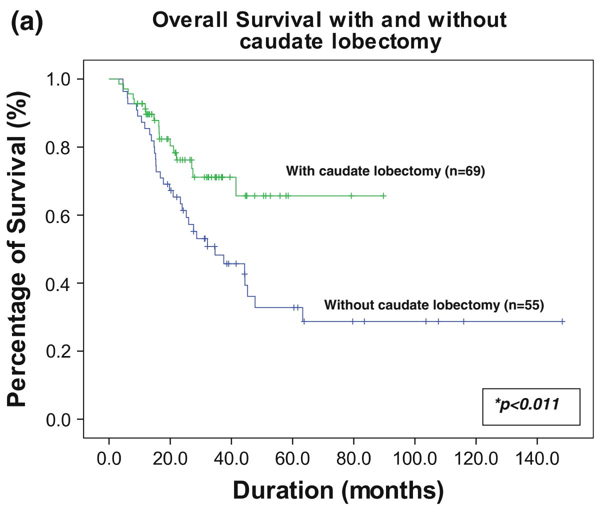
On multivariate analysis, patients who were symptomatic at presentation (HR: 13.417, 95% CI: 1.389–29.647, $p = 0.025$) and positive LN metastasis (HR: 5.928, 95% CI: 2.435–14.429, $p < 0.001$) were significant negative predictors of OS in this study (Fig. 2). Concomitant CL

Table 4 Univariate and multivariate analysis of overall survival of patients with type III_A and III_B hilar cholangiocarcinoma in the study cohort ($n = 124$)

Factor	Univariate analysis			Multivariate analysis		
	HR	95% CI	p value	HR	95% CI	p value
Caudate lobectomy	0.470	0.266–0.832	*0.010	0.471	0.192–0.667	0.068
Age >60 years	0.749	0.436–1.287	0.296			
Operation period after 2005	0.254	0.138–0.468	*0.009	0.535	0.261–0.772	0.120
Presence of biliary stone disease	1.277	0.507–3.217	0.604			
Presence of Clonorchis sinensis	1.597	0.494–5.156	0.434			
Asymptomatic versus symptomatic	5.026	1.561–16.179	*0.007	13.417	1.389–29.647	*0.025
Preoperative bilirubin >3.0 mg/dl	1.537	0.888–2.660	0.124			
Preoperative CA 19-9 > 37.0 U/ml	2.187	1.053–4.540	*0.036	1.069	0.367–3.114	0.902
Preoperative CEA >5.0 U/ml	4.185	1.612–10.865	*0.003	3.060	1.248–7.500	0.221
Portal vein resection	0.920	0.393–2.155	0.848			
Hepatic artery resection	1.898	0.460–7.822	0.375			
Portal vein embolization	0.692	0.249–1.919	0.479			
Bismuth-Corlette (type IIIA vs type IIIB)	0.950	0.496–1.818	0.876			
Left versus right hepatectomy	1.211	0636–2.306	0.560			
Tumor size >5 cm	2.738	1.218–6.154	*0.015	2.864	0.808–10.153	0.103
Stratified T-stage (T1 and T2 vs T3 and T4)	1.796	1.038–3.108	*0.036	1.206	0.517–2.813	0.664
Positive LN metastasis	2.825	1.556–5.126	*0.001	5.928	2.435–14.429	*<0.001
AJCC stage (I and II vs IIIA/B and IVA)	3.668	1.845–7.291	*<0.001			
Positive resection margin	2.099	1.079–4.083	*0.029	1.109	0.339–2.676	0.858
Grade of tumor differentiation	1.005	0.633–1.595	0.983			
Lymphovascular invasion	3.850	1.052–14.088	*0.042	131.089	NR	0.998
Perineural invasion	1.410	0.335–5.930	0.640			

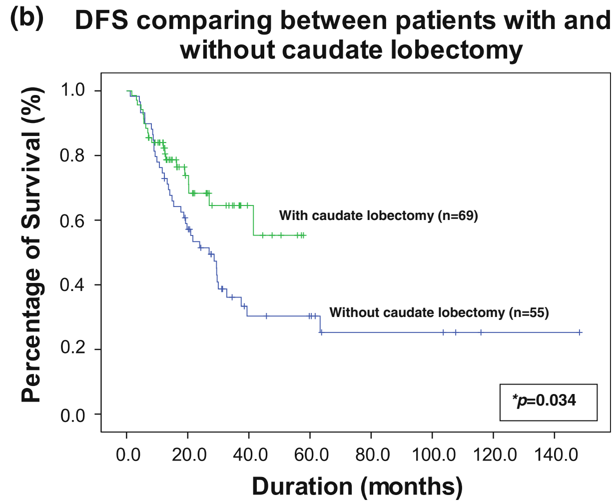
* $p < 0.05$ as statistically significant

HR hazard ratio



	Median (95% CI)	Overall survival (%)			
		1-year	3-year	5-year	7-year
Without CL	34.6 (16.2 – 53.1)	61.0	46.0	30.0	30.0
With CL	64.0 (NR)	76.0	70.0	66.0	66.0

p<0.05* as statistically significant. **95% CI: 95% confidence interval.
CL: Caudate Lobectomy, NR: Not reached



	Median (95% CI)	Disease-free survival (%)		
		1-year	3-year	5-year
Without CL	27.0 (17.9 – 36.1)	75.0	28.0	27.0
With CL	40.5 (NR)	86.0	66.0	57.0 (**4-year**)

p<0.05* as statistically significant. **95% CI: 95% confidence interval.
CL: Caudate Lobectomy, NR: Not reached, DFS: Disease-free Survival.

Fig. 1 Kaplan–Meier curve demonstrating (**a**) overall survival (OS) and (**b**) disease-free survival (DFS) of patients with type III_A and III_B hilar cholangiocarcinoma, comparing between those with and without caudate lobectomy ($n = 124$)

was found to approach statistical significance as a positive prognostic factor for OS (HR: 0.471, 95% CI: 0.192–0.667, $p = 0.068$).

Prognostic factors of disease-free survival (DFS) (Table 5)

The median DFS for patients with CL was 40.5 months compared to 27.0 months in patients without CL ($p = 0.031$) (Fig. 1b). Univariate analysis for DFS using the log-rank test found that caudate lobectomy (HR: 0.341, $p = 0.034$), operative period after 2005 (HR: 1.339, $p = 0.336$), presence of symptoms at presentation (HR: 2.347, $p = 0.018$), elevated preoperative CEA > 5.0 U/ml (HR: 3.968, $p = 0.002$), tumor size > 5 cm (HR: 2.233, $p = 0.026$), positive LN metastasis (HR: 2.325, $p = 0.001$), and grade of tumor differentiation (HR: 1.608, $p = 0.024$) were significant factors associated with disease-free survival.

On Cox proportional hazard regression, caudate lobectomy (HR: 0.341, 95% CI: 0.142–0.818, $p = 0.016$) (Fig. 1b) and positive LN metastasis (HR: 3.546, 95% CI: 1.668–7.539, $p < 0.001$) were found to be prognostic factors of DFS in this study (Fig. 3).

Discussion

Hilar cholangiocarcinoma has a propensity to infiltrate the biliary branches because it is close to the hepatic hilum. Indeed, infiltration into the caudate lobe, particularly in type III and IV hilar cholangiocarcinoma, is fairly common due to the absence of strong muscular layer to restrict the extension of tumors into surrounding biliary radicals [4, 10, 11]. The caudate bile duct usually enters the hepatic duct confluence posteriorly. The reported incidence of caudate bile duct invasion by hilar cholangiocarcinoma ranges from 31.0 to 98.0% in the literature [4, 14, 15]. In a study reported by Sakamoto et al., the pattern of infiltration at the proximal border of the hilar bile duct carcinoma was found to be closely related to the gross tumor type. Submucosal extension is usually less than 10 mm, and superficial spread of carcinoma was seen in more than 10% of their cases. In this respect, Sakamoto et al. [16] recommended that a tumor-free proximal margin of 5 mm was necessary to ensure a satisfactory long-term outcome.

The idea that local resection can adequately treat hilar cholangiocarcinoma is not sustainable in the current state of evidence. Previously, some authors suggested that bile ducts could be resected up to the tertiary branches of the hepatic ducts without liver resection [17, 18]. This coincided with the era when major liver resection was associated with prohibitive risk of morbidity and mortality. However, with improvements in perioperative care and advancements in operative technique for hepatobiliary operations over the last three decades, limited resection of bile duct alone, particularly for type III and IV hilar cholangiocarcinoma, cannot be accepted as adequate curative treatment. Furthermore, the concept of concomitant caudate lobectomy, as popularized

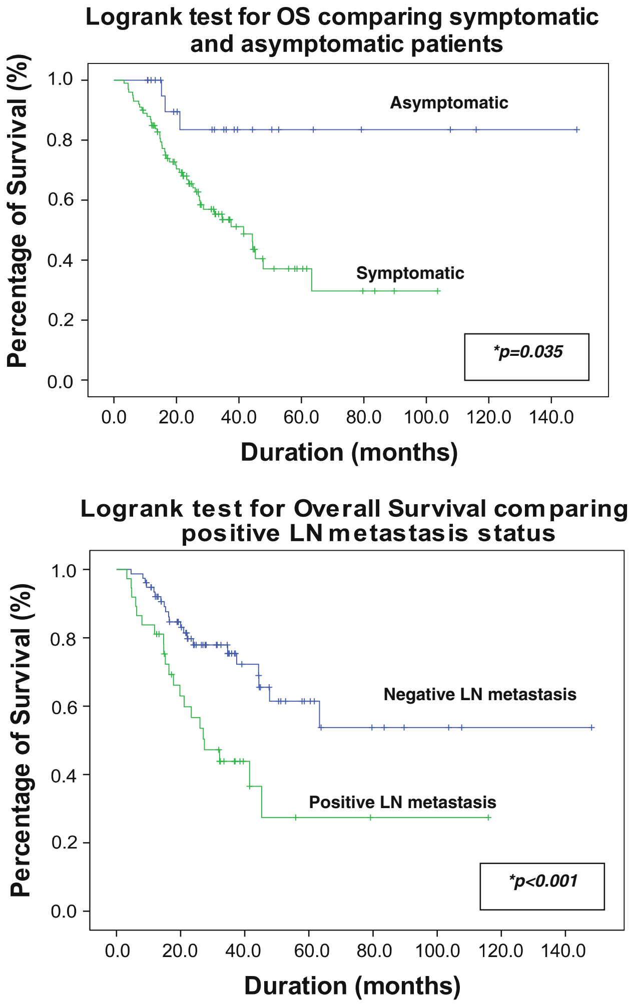


Fig. 2 Kaplan–Meier analysis for prognostic factors for overall survival in type III hilar cholangiocarcinoma ($n = 124$)

by Nimura et al. [4] from Nagoya, has also influenced the trend toward employing surgical resection for hilar cholangiocarcinoma. Such trends are clearly in evidence all over the world. Ercolani et al. [19] from Italy reported a significant increase of the rate of caudate lobe resection in hilar cholangiocarcinoma from 47.1% prior to 1998 to 94.1% in the period after that. Likewise, Dinant et al. [20] from the Netherlands reported 52.0% of concomitant caudate lobectomy after 1998, and this was associated with significantly better R0 resection status.

Much knowledge and experience have been gained over the past three decades regarding the recurrence pattern of hilar cholangiocarcinoma and the clinical behavior of this malignancy. One of the most important factors influencing survival and recurrence is negative resection margin [9, 21]. In our series, the overall R0 resection rate was 89.2%. Although not statistically significantly different, the R1 resection rate in patients without CL was twice (15.8%) that of patients with CL (8.6%). As hilar cholangiocarcinoma is located in the deep recess of the hilum of the liver, extremely close to hepatic vessels and surrounding structures, such as the caudate lobe, curative surgical resection for this malignancy remains a great challenge to hepatobiliary surgeons. In order to obtain negative resection margins, major liver resection has increasingly being accepted as standard treatment [12]. In fact, liver resection that includes caudate lobectomy is often performed, especially in type III and IV (based on the Bismuth-Corlette classification). However, in type IV hilar cholangiocarcinoma, extended liver resection with caudate lobectomy is necessary as both the left and right bile ducts are involved by tumor. On the other hand, in type III_A and III_B cancer, extended liver resection might not be necessary, but the role of caudate lobectomy remains controversial.

In 1986, Mizumoto et al. [22] emphasized that failure to achieve clearance in the caudate lobe could lead to increased risk of tumor recurrence after resection of hilar cholangiocarcinoma. Subsequently, in an autopsy study by Gazzaniga et al., this postulation was affirmed. Gazzaniaga et al. [23] showed that one in five patients in their series had recurrence in the caudate lobe. This increased awareness of and drew attention to the caudate lobe, highlighting the role of resection of caudate lobe in curative resection of hilar cholangiocarcinoma. Further understanding in the relationship of caudate lobe to hilar cholangiocarcinoma was demonstrated in a tumor mapping study by Suzuki et al. [24], which clearly illustrated cancer invasion of the caudate bile duct epithelium in all of the resected specimens. The concept of en bloc caudate lobectomy resection when the confluence is encompassed by hilar cholangiocarcinoma is now widely embraced, not only by Japanese and Korean surgeons, but by Western surgeons as [12, 25–29].

In our study, the OS and DFS were found to be significantly longer in patients with CL as compared to those without CL. The median OS was almost doubled in patients with CL (64.0 vs 34.6 months) while the median DFS was 13.5 months more in patients without CL. Similarly, in one of the early series from Nagoya University Hospital, Nimura et al. reported that the 3- and 5-year survival was 55.1 and 40.5%, respectively, for resection of hilar cholangiocarcinoma including CL. In their cohort, 44 of 45 patients had microscopically proven involvement of caudate branches of bile duct by the hilar cholangiocarcinoma [4]. Likewise, Liu et al., from University of Hong Kong, adopted major hepatectomy with concomitant CL as operative strategy after 1999 for hilar cholangiocarcinoma. On multivariate analysis, they found that this aggressive strategy had significantly improved the overall survival of patients [30]. On this same note, although there were significantly more patients with CL performed after 2005 in our institution, we did not find that the operative period has

Table 5 Univariate and multivariate analysis for disease-free survival for patients in the study cohort ($n = 124$)

Factor	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Caudate lobectomy	0.554	0.321–0.956	*0.034	0.341	0.142–0.818	*0.016
Age >60 years	0.908	0.578–1.424	0.908			
Operation period after 2005	1.339	0.739–2.426	0.336			
Presence of biliary stone disease	1.219	0.558–2.663	0.619			
Presence of Clonorchis sinensis	0.918	0.287–2.931	0.885			
Asymptomatic versus symptomatic	2.347	1.159–4.754	*0.018	2.243	0.501–10.033	0.291
Preoperative bilirubin mg/dl >3.0	1.117	0.710–1.757	0.632			
Preoperative CA 19-9 U/ml > 37.0	1.472	0.855–2.533	0.163			
Preoperative CEA U/ml >5.0	3.968	1.660–9.487	*0.002	2.141	0.347–13.226	0.412
Portal vein resection	1.055	0.525–2.118	0.881			
Hepatic artery resection	1.596	0.389–6.551	0.516			
Portal vein embolization	0.763	0.350–1.662	0.496			
Bismuth-Corlette (type IIIA vs type IIIB)	1.018	0.611–1.696	0.945			
Left versus right hepatectomy	0.923	0.558–1.525	0.754			
Tumor size >5 cm	2.233	1.103–4.520	*0.026	1.605	0.322–8.012	0.564
Stratified T-stage (T1 and T2 vs T3 and T4)	1.488	0.931–2.377	0.097			
Positive LN metastasis	2.325	1.433–3.774	*0.001	5.077	2.133–12.094	*<0.001
Stratified AJCC stage (I and II vs IIIA/B and IVA)	2.377	1.434–3.940	*0.001			
Positive resection margin	1.225	0.661–2.269	0.520			
Grade of tumor differentiation	1.608	1.064–2.430	*0.024	1.946	0.955–3.950	0.067
Lymphovascular invasion	1.109	0.445–2.762	0.825			
Perineural invasion	0.898	0.319–2.526	0.839			

* $p < 0.05$ as statistically significant

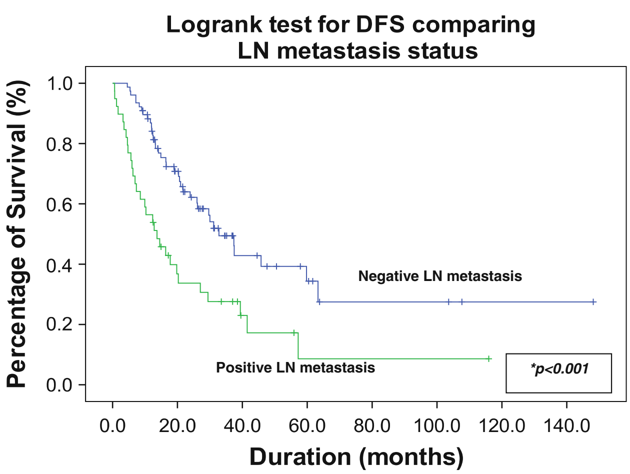


Fig. 3 Prognostic factor for disease-free survival for patients with type III hilar cholangiocarcinoma ($n = 124$)

a significant impact on the OS and DFS, but CL was an independent prognostic factor for better survival on multivariate analysis.

Many studies have identified predictive factors associated with OS in hilar cholangiocarcinoma after curative resection, including resection margin status, lymph node metastasis, preoperative chemotherapy, perineural invasion, tumor size, histology differentiation, tumor stage, and caudate lobe [30–33]. In comparison, this study found that presence of symptom at presentation and positive lymph node metastasis were significant negative prognostic factor for overall survival. At the same time, caudate lobectomy was approaching statistical significance as a positive prognostic factor for OS on multivariate analysis. On top of that, caudate lobectomy was a significant positive prognostic factor, while positive lymph node metastasis was significant negative prognostic factor for DFS on multivariate analysis. Caudate lobectomy in the treatment of type III hilar cholangiocarcinoma resulted in better DFS but had a less significant effect on the OS, probably because the tumor behaved aggressively once recurrence was detected in the patients.

Conclusions

Caudate lobectomy contributed to improvement of DFS and OS in type III_A and III_B hilar cholangiocarcinoma. It should be considered part of a standard surgical resection in this subgroup of patients. Other prognostic factors for OS and DFS in this study include positive LN metastasis and presence of symptoms.

Conflict of interest None.

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